

WHAT IS CLAIMED IS:

1. A method for controlling excessive proliferation or migration of smooth muscle cells comprising treating said smooth muscle cells with an effective amount of an antagonist of a native ErbB4 receptor.

5 2. The method of claim 1 wherein the control is prevention of excessive proliferation or migration of smooth muscle cells.

3. The method of claim 1 wherein the control is inhibition of excessive proliferation or migration of smooth muscle cells.

4. The method of claim 3 wherein said inhibition is total inhibition.

10 5. The method of claim 1 wherein said smooth muscle cells are pyloric smooth muscle cells.

6. The method of claim 1 wherein said smooth muscle cells are urinary bladder smooth muscle cells.

7. The method of claim 1 wherein said smooth muscle cells are those of an airway passage.

8. The method of claim 1 wherein said excessive proliferation or migration of smooth muscle cells results in stenosis.

9. The method of claim 1 wherein said smooth muscle cells are vascular smooth muscle cells.

10. The method of claim 9 wherein said vascular smooth muscle cells are human.

11. The method of claim 9 wherein said vascular smooth muscle cells are human aortic smooth muscle cells.

12. The method of claim 9 wherein said excessive proliferation or migration of smooth muscle cells results in vascular stenosis.

25 13. The method of claim 12 wherein said vascular stenosis is further characterized by excessive proliferation or migration of endothelial cells.

14. The method of claim 13 wherein said stenosis is restenosis.

15. The method of claim 1 wherein the ErbB4 receptor antagonist is an immunoadhesin.

16. The method of claim 15 wherein said immunoadhesin comprises an extracellular domain sequence of a native ErbB4 receptor.

17. The method of claim 16 wherein said native ErbB4 receptor is human.

5 18. The method of claim 17 wherein the native human ErbB4 receptor extracellular domain sequence is fused to an immunoglobulin heavy chain constant region sequence.

19. The method of claim 18 wherein said immunoglobulin is of IgG isotype.

20. The method of claim 19 wherein said immunoglobulin is of IgG1, IgG2 or IgG3 isotype.

10 21. The method of claim 19 wherein said immunoadhesin comprises at least one IgG immunoglobulin light chain.

22. The method of claim 1 wherein said antagonist is an antibody.

15 23. The method of claim 22 wherein said antibody is a neutralizing antibody against a native ErbB4 receptor.

20 24. The method of claim 23 wherein said antibody is a chimeric, humanized or human antibody.

25 25. The method of claim 23 wherein said antibody is glycosylated.

26. The method of claim 23 wherein said antibody binds essentially the same epitope as an antibody produced by a hybridoma selected from the group consisting of HER4.10H1.1A1 (ATCC Accession Number PTA-2828), HER4.1C6.A11 (ATCC Accession Number PTA-2829), HER4.3B9.2C9 (ATCC Accession Number PTA-2826), HER4.1A6.5B3 (ATCC Accession Number PTA-2827) and HER4.8B1.2H2 (ATCC Accession Number PTA-2825).

27. The method of claim 23 wherein said antibody has complementarity determining region (CDR) residues from an antibody produced by a hybridoma selected from the group consisting of HER4.10H1.1A1 (ATCC Accession Number PTA-2828), HER4.1C6.A11 (ATCC Accession Number PTA-2829), HER4.3B9.2C9 (ATCC Accession Number PTA-2826), HER4.1A6.5B3 (ATCC Accession Number PTA-2827) and HER4.8B1.2H2 (ATCC Accession Number PTA-2825).

28. A method for treating stenosis in a mammalian patient comprising administering to said patient an effective amount of an antagonist of a native mammalian ErbB4 receptor.

29. The method of claim 28 wherein said patient is human.

5 30. The method of claim 29 wherein said stenosis is vascular stenosis.

31. The method of claim 30 wherein said vascular stenosis is restenosis.

32. The method of claim 28 wherein said antagonist is an immunoadhesin.

33. The method of claim 32 wherein said immunoadhesin comprises an extracellular domain sequence of a native human ErbB4 receptor.

10 34. The method of claim 33 wherein said extracellular domain sequence is fused to an immunoglobulin heavy chain constant region sequence.

35. The method of claim 34 wherein said immunoglobulin is of IgG isotype.

36. The method of claim 28 wherein said antagonist is an antibody.

37. The method of claim 36 wherein said antibody is a neutralizing antibody against a native human ErbB4 receptor.

38. The method of claim 36 wherein said antibody binds essentially the same epitope as an antibody produced by a hybridoma selected from the group consisting of HER4.10H1.1A1 (ATCC Accession Number PTA-2828), HER4.1C6.A11 (ATCC Accession Number PTA-2829), HER4.3B9.2C9 (ATCC Accession Number PTA-2826), HER4.1A6.5B3 (ATCC Accession Number PTA-2827) and HER4.8B1.2H2 (ATCC Accession Number PTA-2825).

39. The method of claim 36 wherein said antibody has complementarity determining region (CDR) residues from an antibody produced by a hybridoma selected from the group consisting of HER4.10H1.1A1 (ATCC Accession Number PTA-2828), HER4.1C6.A11 (ATCC Accession Number PTA-2829), HER4.3B9.2C9 (ATCC Accession Number PTA-2826), HER4.1A6.5B3 (ATCC Accession Number PTA-2827) and HER4.8B1.2H2 (ATCC Accession Number PTA-2825).

25 40. The method of claim 28 wherein said antagonist is administered as an injection or infusion.

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41. The method of claim 28 wherein said treatment additionally reduces hypertension associated with said stenosis.
42. The method of claim 28 wherein said treatment is prevention.
43. The method of claim 28 wherein said stenosis is pyloric stenosis.
44. The method of claim 28 wherein said stenosis is thickening of the urinary bladder wall.
45. The method of claim 28 wherein said stenosis is part of an obstructive airway disease.
46. A method for treating stenosis in a mammalian patient comprising introducing into a cell of said patient a nucleic acid encoding an antagonist of an ErbB4 receptor.
47. The method of claim 46 wherein said patient is human.
48. The method of claim 47 wherein said antagonist is an immunoadhesin.
49. The method of claim 48 wherein said immunoadhesin comprises an extracellular domain sequence of a native human ErbB4 receptor fused to an immunoglobulin heavy chain constant region sequence.
50. The method of claim 47 wherein said antagonist is an antibody.
51. The method of claim 50 wherein said antibody is a neutralizing antibody against a native ErbB4 receptor.
52. The method of claim 51 wherein said antibody is a chimeric, humanized or human antibody.
53. The method of claim 51 wherein said antibody binds essentially the same epitope as an antibody produced by a hybridoma selected from the group consisting of HER4.10H1.1A1 (ATCC Accession Number PTA-2828), HER4.1C6.A11 (ATCC Accession Number PTA-2829), HER4.3B9.2C9 (ATCC Accession Number PTA-2826), HER4.1A6.5B3 (ATCC Accession Number PTA-2827) and HER4.8B1.2H2 (ATCC Accession Number PTA-2825).
54. The method of claim 51 wherein said antibody has complementarity determining region (CDR) residues from an antibody produced by a hybridoma selected from the group consisting of HER4.10H1.1A1 (ATCC Accession Number PTA-2828), HER4.1C6.A11 (ATCC Accession Number PTA-2829), HER4.3B9.2C9 (ATCC Accession

Number PTA-2826), HER4.1A6.5B3 (ATCC Accession Number PTA-2827) and HER4.8B1.2H2 (ATCC Accession Number PTA-2825).

55. The method of claim 46 wherein said nucleic acid is introduced *in vivo*.

56. The method of claim 46 wherein said nucleic acid is introduced *ex vivo*.

5 57. A method for treating hypertension associated with vascular stenosis in a mammalian patient, comprising administering to said patient an effective amount of an antagonist of a native mammalian ErbB4 receptor.

58. The method of claim 57 wherein said antagonist is a small molecule.

10 59. A pharmaceutical composition for the treatment of stenosis in a mammalian patient comprising an effective amount of an antagonist of a native mammalian ErbB4 receptor, in admixture with a pharmaceutically acceptable carrier.

60. A method for identifying a molecule that inhibits or enhances the proliferation or migration of smooth muscle cells, comprising the steps of:

(a) contacting a polypeptide comprising an amino acid sequence having at least 85 % sequence identity with the amino acid sequence of the extracellular domain of a native ErbB4 receptor and retaining the ability to control excessive proliferation or migration of smooth muscle cells, with a candidate molecule; and

(b) determining whether the candidate molecule inhibits or enhances the ability of said polypeptide to control excessive proliferation or migration of smooth muscle cells.

20 61. The method of claim 60 wherein said polypeptide comprises the extracellular domain of a native ErbB4 receptor.

62. The method of claim 61 wherein said receptor is human.

63. The method of claim 61 wherein said polypeptide is an immunoadhesin.

25 64. The method of claim 60 wherein said molecule enhances the ability of said polypeptide to control excessive proliferation or migration of smooth muscle cells.

65. The method of claim 64 wherein said molecule is selected from the group consisting of antibodies and small molecules.

30 66. An antibody that binds essentially the same epitope of ErbB4 as an antibody produced by a hybridoma selected from the group consisting of HER4.10H1.1A1 (ATCC Accession Number PTA-2828), HER4.1C6.A11 (ATCC Accession Number PTA-2829),

HER4.3B9.2C9 (ATCC Accession Number PTA-2826), HER4.1A6.5B3 (ATCC Accession Number PTA-2827) and HER4.8B1.2H2 (ATCC Accession Number PTA-2825).

67. An antibody that has complementarity determining region (CDR) residues from an antibody produced by a hybridoma selected from the group consisting of HER4.10H1.1A1 (ATCC Accession Number PTA-2828), HER4.1C6.A11 (ATCC Accession Number PTA-2829), HER4.3B9.2C9 (ATCC Accession Number PTA-2826), HER4.1A6.5B3 (ATCC Accession Number PTA-2827) and HER4.8B1.2H2 (ATCC Accession Number PTA-2825).

68. An antibody selected from the group consisting of an antibody produced by a hybridoma selected from the group consisting of HER4.10H1.1A1 (ATCC Accession Number PTA-2828), HER4.1C6.A11 (ATCC Accession Number PTA-2829), HER4.3B9.2C9 (ATCC Accession Number PTA-2826), HER4.1A6.5B3 (ATCC Accession Number PTA-2827) and HER4.8B1.2H2 (ATCC Accession Number PTA-2825).

69. An antibody that binds essentially the same epitope of ErbB4 bound by an antibody selected from the group consisting of anti-ErbB4 monoclonal antibodies 4-1440, 4-1460, 4-1473, 4-1492 and 4-1464.

70. An antibody that has complementarity determining region (CDR) residues from an antibody selected from the group consisting of anti-ErbB4 monoclonal antibodies 4-1440, 4-1460, 4-1473, 4-1492 and 4-1464.

71. An antibody which binds to ErbB4 with high affinity.

72. The antibody of claim 71 which binds to ErbB4 with a Kd of less than 100 nM.

73. The antibody of claim 71 which binds to ErbB4 with a Kd of less than 50 nM.

74. The antibody of claim 71 which binds to ErbB4 with a Kd of less than 10 nM.

75. The antibody of claim 71 which is a humanized antibody.

76. The antibody of claim 71 which is a human antibody.

77. The antibody of claim 71 which is an antibody fragment.

78. An antibody which is capable of binding to both ErbB4 and ErbB3.

79. The antibody of claim 78 which binds ErbB4 with high affinity.

80. The antibody of claim 78 which binds both ErbB4 and ErbB3 with high affinity.
81. An antibody which binds to ErbB4 and reduces heregulin binding thereto.
82. The antibody of claim 81 which binds ErbB4 with high affinity.
- 5      83. An antibody which binds to ErbB4 and reduces heregulin-induced tyrosine phosphorylation thereof.
84. The antibody of claim 83 which binds ErbB4 with high affinity.